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(54) Biocompatible polyurea-urethane hydrated polymers

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Polymères hydratés de polyurée-uréthane biocompatibles

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Description**BACKGROUND OF THE INVENTION**

- 5 This invention relates to synthetic hydrated polymers in the form of coatings, impregnants and gels. More specifically, a unique series of crosslinked polyurea-urethane polymer gels can be formed from high molecular weight isocyanate end-capped prepolymers which are substantially comprised of ethylene oxide units. These hydrophilic polymers are characterized by their biocompatibility and by their exhibiting a unique surface which resists nonspecific protein adsorption.
- 10 Numerous polyurethane polymers have been previously identified, among them both foamed and nonfoamed materials. Of the nonfoamed materials, quite a few hydrogel polymers, prepared from various prepolymers, have been prepared and used for widely varying applications. Typically, hydrogels are formed by polymerizing a hydrophilic monomer in an aqueous solution under conditions such that the prepolymer becomes crosslinked, forming a three-dimensional polymeric network which gels the solution. Polyurethane hydrogels are formed by polymerization of isocyanate-end capped prepolymers to create urea and urethane linkages.

15 Representative examples of previously disclosed polyurethane hydrogels include the following:

- 20 U.S. 4,241,537 (Wood) discloses a plant growth media comprising a hydrophilic polyurethane gel composition prepared from chain-extended polyols; random copolymerization is preferred with up to 50% propylene oxide units so that the prepolymer will be a liquid at room temperature. U.S. 3,939,123 (Matthews) discloses lightly crosslinked polyurethane polymers of isocyanate terminated prepolymers comprised of poly(ethyleneoxy) glycols with up to 35% of a poly(propyleneoxy) glycol or a poly(butyleneoxy) glycol. In producing the Matthews prepolymer, the ratio of isocyanato groups to hydroxyl is from 1.2 to 1.6 equivalents of isocyanato per equivalent of hydroxyl. A solids content of 25 to 40 wt.% is employed in forming the hydrogel. U.S. 4,118,354 (Harada) discloses a polyurethane hydrogel prepared from the reaction product of a polyisocyanate with a polyether which comprises a plurality of alkylene oxides, 50 to 90% by weight of which is ethylene oxide, added at random to a polyalcohol having at least two terminal hydroxyl groups. Harada requires that the prepolymers be liquid or pasty at room temperature in order to avoid having to liquify the prepolymer either by heating it or diluting it with a solvent. U.S. 4,381,332 (Fulmer et al.) discloses a polyurethane gel adhesive to form a nonwoven fabric, prepared from a prepolymer having molecular weight of at least 3000, made from an aliphatic polyisocyanate capped polyether polyol; up to 50% may be butylene oxide and propylene oxide. U.S. 3,719,050 (Asao) teaches a soil stabilization method in which a polyurethane prepolymer having terminal isocyanate groups is injected into the ground; the prepolymer may be diluted with water or may be reacted with water present in or flowing through the soil.
- 25 US-A-4 209 605 discloses a process for producing lightly crosslinked, hydrogel polymers wherein a poly(oxyalkylene)polyol is reacted with an organic polyisocyanate, thereby producing an isocyanate terminated prepolymer.

30 It can be seen that numerous combinations of molecular weights and prepolymer composition have been patented. Typically, prior hydrogel systems have required that the polyols and prepolymers be liquid or pasty at room temperatures to avoid having to melt the composition. This requirement places restraints on the composition of the polyols and prepolymers. As a rule, the prior art teaches copolymerization of propylene oxide or butylene oxide units sufficient to yield liquid polyols and prepolymers. However, inclusion of these monomer units also serves to decrease the hydrophilicity of the prepolymer. Additionally, low molecular weight prepolymers have been used to achieve this end.

35 In addition, biocompatibility is an increasingly desirable characteristic for polymeric hydrogels and hydrated polymers, which would find numerous uses in the health care field if the appropriate properties can be obtained. However, many conventional hydrogels are not taught to be biocompatible.

40 Finally, prior art hydrogels tend to adsorb proteins from solutions with which they are brought into contact. This is a particular problem in attempting to utilize polymeric hydrogels for health care applications where proteins are omnipresent. The result may be occlusion or clogging of the polymer, clouding, contamination, irritation to adjacent body tissues, or loss of tissue or bodily fluid protein by irreversible adsorption or denaturation. When such hydrogels are 45 used in contact with the bloodstream, thrombogenesis, complement activation or calcium deposition may result.

SUMMARY OF THE INVENTION

50 The polyurethane polymer system of this invention provides hydrated polymer gels with highly desirable properties which make them particularly well suited for use in the growing field of biomedical applications for polymers. The polymers of this invention are prepared from an aqueous solution of a high molecular weight isocyanate end-capped prepolymer substantially or exclusively comprised of ethylene oxide units. These hydrated polymers may take the typical form of water-swellable hydrogels, or they may take the form of a dense or thin coating or impregnant on a

substrate, including, under dilute conditions, a monomolecular or substantially monomolecular layer. The coatings and impregnates of this invention are considered gels or hydrogels and are included by those terms unless otherwise noted. The terms gel or hydrogel are meant to refer to polymers which are non-foamed in structure.

It is one of the primary objects of this invention to provide a class of hydrated polymers for which preparation and handling is combined with desirable properties permitting a wide range of end uses. In this regard, the novel prepolymers disclosed herein can be handled and stored in liquid form at ambient temperatures even though the relatively high molecular weight prepolymers, which comprise a very high proportion of ethylene oxide units, and the polyols from which they are prepared, are often solid at ambient temperatures. This significantly facilitates formation of the hydrated polymer, as well as enhances the uniformity of the polymer.

It is a related object of the invention to provide a class of polyurea-urethane prepolymers and related hydrated polymers which are hydrophilic, transparent and biocompatible.

It is further object to provide polymeric surfaces which are hydrophilic and yet display marked resistance to the nonspecific adsorption of proteins.

The above objects/problems are solved by a crosslinked hydrophilic, biocompatible hydrated polymer gel prepared by reacting together water and a prepolymer in a prepolymer-to-water ratio of 1:1 to 1:20, said prepolymer being prepared by:

(a) selecting diols or polyols having molecular weights of 7000 to 30,000, at least 75% of which are oxyethylene-based, and

(b) reacting said diols or polyols with polyisocyanate at an isocyanate-to-hydroxyl ratio of 1.8 to 2.2 so that essentially all of the hydroxyl groups of said diols or polyols are capped with polyisocyanate and the resulting prepolymer has an isocyanate concentration of 0.1 to 0.47 meq/g,

said hydrated polymer being characterized by transparency and by a surface which resists nonspecific protein adsorption.

DETAILED DESCRIPTION OF THE INVENTION

A new class of hydrophilic polyurethane prepolymers and related crosslinked hydrated polymer gels has been found which are uniquely characterized by biocompatibility and resistance to nonspecific protein adsorption. The hydrated polymers are formed from polymeric monomer units (the prepolymer units) which are diols or polyols having molecular weights of 7000 to 30,000, at least 75% of which are oxyethylene-based, with essentially all of the hydroxyl groups of these diols or polyols capped with polyisocyanates. Polymerization of the prepolymer (the isocyanate-capped diol or polyol) in water or an aqueous solution acts to gel the solution or a deposited layer of the composition. The prepolymers useful in this invention are prepared by reacting the selected diols or polyols with polyisocyanate at an isocyanate-to-hydroxyl ratio of 1.8 to 2.2 so that essentially all of the hydroxyl groups of the polyols are capped with polyisocyanate.

The diols and polyols used in this invention predominantly or exclusively are polyoxyalkylene diols or polyols made up of ethylene oxide monomer units. At least 75% of the units should be ethylene oxide, preferably at least 90%, and more preferably at least 95%. Most preferably, substantially all or all of the units should be ethylene oxide. Conventional urethane polymer hydrogel systems typically require inclusion of substantial proportions of propylene oxide or butylene oxide units in the polyols and derivative prepolymers to ensure that they will be liquid or pasty at room temperature. Alternatively, solid or crystalline polyols and derivative prepolymers must be heated to their melting point in order to be handled for use in conventional systems. These requirements are avoided by the present invention. Even 100% ethylene oxide diols or polyols and the derivative prepolymers may be accommodated. Extremely high ethylene oxide content (i.e., greater than 90 or 95%) is in fact preferred, with 100% ethylene oxide-based diols or polyols and derivative prepolymers being the most preferred for this invention.

High molecular weight ethylene oxide-based diols and polyols are used to prepare the prepolymers and hydrated polymers of the present invention. The diol or polyol molecular weight prior to capping with polyisocyanate is at least 7000 to 8000 MW, preferably 10,000 to 20,000 MW. It is preferred to use trihydroxy compounds (triols) in the preparation of the polyols which are the precursors to the prepolymers and hydrated polymers of this invention. For example, glycerol is a preferred triol. Trimethylolpropane (TMOP), trimethylolethane and triethanolamine are other suitable triols. In addition, tetrols, such as pentaerithritol, may be used to prepare polyols for use in this invention. Triol- or tetrol-based polyols are capped with difunctional or polyfunctional isocyanate compounds as described below to form the prepolymer.

Alternatively, diols of appropriate molecular weight may be used as precursors to the prepolymers of this invention. Diols of appropriate molecular weight are capped with polyfunctional isocyanates as described below to form the pre-

polymers. High molecular weight polyethylene glycols are particularly useful. Especially desirable in this embodiment are polyethylene glycols of the formula $H(OCH_2CH_2)_xOH$ where x is an average number such that the glycol has an average molecular weight of at least 7000, preferably 10,000 to 30,000. Alternatively, diols may be capped with diisocyanates and used in conjunction with crosslinking compounds to form the hydrated polymers described herein.

5 Crosslinking compounds useful for this purpose include polyfunctional amines and polyfunctional isocyanates. In still another alternative embodiment, diols may be mixed with polyols and the resulting mixture reacted with isocyanates to produce the prepolymer of this invention.

The prepolymers of this invention are formed by reacting the hydroxyl groups of the diols or polyols described above with polyisocyanates. "Polyisocyanate" as used herein is intended to refer to both diisocyanates and polyisocyanates, as appropriate, except as indicated by specifying the use of difunctional or polyfunctional isocyanates. Iso-
10 cyanate end-capped (i.e., isocyanate-terminated) prepolymers are formed. The choice of the polyisocyanate will depend on such factors as selection of the precursor to the prepolymer (i.e., polyol or diol), the degree of handling or shaping required in preparing the polymer, and the anticipated end use of the hydrated, crosslinked polymeric structure.

The selected precursor to the prepolymer influences the choice of polyisocyanate in that the prepolymer structure
15 must lend itself to sufficient crosslinking to gel an aqueous prepolymer solution or to form a crosslinked polymeric coating. In the embodiment in which the precursors to the prepolymers are polyols (that is, triol-based or tetrol-based), difunctional isocyanates are preferred. If desired, polyfunctional isocyanate compounds may also be used with polyols. Mixtures of suitable isocyanates also may be considered.

Where diols are used as the precursors to the prepolymers, they may be reacted with polyfunctional isocyanate
20 compounds to form the prepolymers of this invention. This combination yields prepolymers having sufficient functional groups for crosslinking in the formation of the hydrated polymer. In an alternative embodiment using diols as the precursors to the prepolymers, the diols may be capped with a difunctional isocyanate. In order to achieve sufficient crosslinking in the hydrated polymer prepared from these difunctional prepolymers, they are used in conjunction with a crosslinking compound. The preferred crosslinker is trimethylolpropane ("TMOP"), although others may be used, for example, glycerol, trimethylolethane, pentaerythritol, triethanolamine, polyfunctional amines and polyfunctional isocyanates.

Aromatic, aliphatic or cycloaliphatic polyisocyanates may be used in any of the above-described embodiments. The use of aliphatic polyisocyanates permits a greater degree of handling and/or shaping since aliphatic isocyanate-capped prepolymers typically require about 20 to 90 minutes to gel to a hydrated polymer state. By contrast, prepolymers capped with aromatic polyisocyanates will gel more rapidly, in about 30 to 60 seconds. In addition, aliphatic polyisocyanates will be preferred when the hydrated polymer is intended to be used in medical applications, because of decreased toxicological considerations. However, hydrated polymers made using aromatic polyisocyanates in the prepolymer are also useful, as well as being suitable for most industrial uses.

Examples of suitable di- and polyfunctional isocyanates are found in the following list:

35 toluene-2,4-diisocyanate
 toluene-2,6-diisocyanate
 commercial mixtures of toluene-2,4 and 2,6-diisocyanates
 isophorone diisocyanate
 40 ethylene diisocyanate
 ethylidene diisocyanate
 propylene-1,2-diisocyanate
 cyclohexylene-1,2-diisocyanate
 cyclohexylene-1,4-diisocyanate
 45 m-phenylene diisocyanate
 3,3'-diphenyl-4,4'-biphenylene diisocyanate
 4,4'-biphenylene diisocyanate
 4,4'-diphenylmethane diisocyanate
 3,3'-dichloro-4,4'-biphenylene diisocyanate
 50 1,6-hexamethylene diisocyanate
 1,4-tetramethylene diisocyanate
 1,10-decamethylene diisocyanate
 cumene-2,4-diisocyanate
 1,5-naphthalene diisocyanate
 55 methylene dicyclohexyl diisocyanate
 1,4-cyclohexylene diisocyanate
 p-tetramethyl xylylene diisocyanate
 p-phenylene diisocyanate

4-methoxy-1,3-phenylene diisocyanate
 4-chloro-1,3-phenylene diisocyanate
 4-bromo-1,3-phenylene diisocyanate
 4-ethoxy-1,3-phenylene diisocyanate
 5 2,4-dimethyl-1,3-phenylene diisocyanate
 5,6-dimethyl-1,3-phenylene diisocyanate
 2,4-diisocyanatodiphenylether
 4,4'-diisocyanatodiphenylether
 benzidine diisocyanate
 10 4,6-dimethyl-1,3-phenylene diisocyanate
 9,10-anthracene diisocyanate
 4,4'-diisocyanatodibenzyl
 3,3'-dimethyl-4,4'-diisocyanatodiphenylmethane
 2,6-dimethyl-4,4'-diisocyanatodiphenyl
 15 2,4-diisocyanatostilbene
 3,3'-dimethoxy-4,4'-diisocyanatodiphenyl
 1,4-anthracenediisocyanate
 2,5-fluorenediisocyanate
 1,8-naphthalene diisocyanate
 20 2,6-diisocyanatobenzfuran
 2,4,6-toluene triisocyanate
 p,p',p"-triphenylmethane triisocyanate
 trifunctional trimer (isocyanurate) of isophorone diisocyanate
 trifunctional biuret of hexamethylene diisocyanate
 25 trifunctional trimer (isocyanurate) of hexamethylene diisocyanate
 polymeric 4,4'-diphenylmethane diisocyanate.

Capping of the selected diols or polyols with polyisocyanates to form the prepolymers of this invention is effected using stoichiometric amounts of reactants. The isocyanate-to-hydroxyl group ratio preferably is between 1.8 and 2.2.

30 The capping reaction may be by any convenient method or procedure. For example, the reaction may be carried out at 20 to 150°C, under dry nitrogen, for 2 hours to 14 days, preferably in the absence of a catalyst. The preferred temperature is 60 to 70°C. The reaction is terminated when the isocyanate concentration approaches theoretical values. The time period will be a function of the polyisocyanate used and the temperature at which the reaction is conducted. Polymerization occurs much more rapidly when aromatic polyisocyanates are used than with aliphatic polyisocyanates.

35 Similarly, the reaction will be more rapid with increased temperatures.

It is preferred to avoid using an excess of polyisocyanate in preparing the prepolymer. Preferably, an isocyanate-to-hydroxyl group ratio of 2:1 (for example, one diisocyanate molecule per hydroxyl group of the polyol) is used to ensure complete end-capping of the polyol. Complete end-capping eliminates excessively high viscosity in the prepolymer by avoiding undue amounts of chain extension. However, a slight excess of isocyanate, i.e., up to about ten percent, can be used.

40 It is characteristic of the present polymer system that the isocyanate content is very low. This is achieved by employing high molecular weight polyols and by avoiding excessive quantities of isocyanate in the end-capping reaction so that free isocyanate monomers are unlikely to be present. The isocyanate concentration in the prepolymer is 0.1 to 0.47 milliequivalents per gram, for prepolymers formed from diols or polyols of 7,000 to 30,000 MW.

45 Notwithstanding a preference for low isocyanate content, the polymer system described herein affords a greater degree of flexibility in this regard than conventional systems. The presence of the organic solvent in preparing and handling the prepolymer protects against excessive viscosity resulting from the use of insufficient quantities of isocyanate for complete end-capping of the diol or polyol. That is, it permits the use of less than stoichiometric (2:1) quantities of the isocyanate monomer. Chain extension resulting from incomplete end-capping typically results in increased viscosity which may make handling of the prepolymer difficult or impossible. By contrast, the system of this invention tends not to be affected negatively by increased viscosity due to chain extension, or from any other cause, because the solvent serves to maintain the viscosity within a range suitable for convenient handling of the prepolymer.

50 The organic solvent used in preparing the prepolymer must be compatible with the reactants and with the end use desired for the hydrated polymer. Primarily, the solvent must be one in which the diol or polyol and/or prepolymer can be readily dissolved, preferably at ambient temperatures. Suitable solvents for preparing the prepolymer include acetonitrile, dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, dioxane, dichloromethane, acetone and methyl ethyl ketone, or mixtures thereof. Acetonitrile is preferred.

55 In one embodiment using an organic solvent, the diol or polyol itself is dissolved in the solvent and is reacted with

polyisocyanate while in solution to yield the isocyanate end-capped prepolymer. This embodiment is particularly preferred where the diol or polyol is solid or crystalline at ambient temperatures, that is, for diols or polyols substantially or exclusively comprised of ethylene oxide units and for high molecular weight diols or polyols. In this manner, even crystalline diols or polyols can easily be handled without heating to their respective melting points. Even though the prepolymer formation reaction is conducted at elevated temperatures, utilizing an organic solvent to first place the diol or polyol in liquid form assures good reaction and prepolymer formation.

In another embodiment using an organic solvent, the isocyanate end-capped prepolymer first is prepared and then is dissolved in an organic solvent. This embodiment will be useful where the diol or polyol already is liquid or pasty at ambient temperatures and does not require dissolution in order to prepare the prepolymer. For example, diols or polyols of lower molecular weight or higher propylene oxide or butylene oxide content may be treated in this manner. Use of a solvent at the prepolymer stage is advantageous where increased viscosity occurs due to chain extension of incompletely end-capped diols or polyols.

In addition, organic solvents are useful in preparing the hydrated polymer of this invention. During polymerization, the presence of a solvent enables the system to tolerate higher levels of excess isocyanate (over stoichiometric amounts) without causing disruption of the hydrated polymer formation. Carbon dioxide formed by the reaction of excess isocyanate monomer and water simply effervesces due to the system's low viscosity, rather than becoming entrapped to elicit foam formation. The solvents listed above as being suitable for use in preparing the prepolymer may also be used here. In addition, methanol, ethanol, 2-propanol and dichloromethane, or mixtures thereof, may be used. However, if methanol is selected, it must be removed promptly (i.e., within a few minutes to several hours) in order to avoid excessive end capping of the isocyanate groups, which will prevent polymerization.

If an organic solvent is used in the preparation of the prepolymer or hydrated polymer, it most frequently will be removed prior to use of the polymer. The solvent may be removed from the prepolymer prior to curing or may be allowed to evaporate during the process of depositing or coating the prepolymer onto a desired coatable substrate or forming the prepolymer into the desired shape. Alternatively, where a thin polymeric coating is desired, the prepolymer may be adsorbed onto a substrate directly from the solvent solution after which the entire coated substrate may be removed from the solvent. In most cases where curing is accomplished in the presence of the solvent, the solvent is removed from the hydrated polymer after curing, either by evaporation or by washing with water. In these cases, it is necessary to use a solvent which is water soluble. The organic solvent-prepolymer solution then will be compatible with the aqueous solution in which the hydrated polymer will be formed, resulting in an aqueous prepolymer solution, not an emulsion or dispersion.

It may be desired to add an antioxidant agent at some point prior to polymerization, preferably prior to preparation of the prepolymer. Antioxidants are not required to make or use the prepolymers or hydrated polymers of this invention. However, storage and handling properties may be enhanced by such an addition by preventing oxidative breakdown of the polymer or its precursors. Suitable antioxidants include the hindered phenolic compounds. Specific examples are Irganox (TM) (Ciba-Geigy Corp.) and Santonox (TM) (Monsanto Chemical Co.). The antioxidant may be added in amounts of 0.01 to 1.0%, preferably 0.02 to 0.1%, based on the weight of the polyol or precursor to the prepolymer.

Gelling or curing is accomplished by the addition of a stoichiometric excess of water or aqueous solution, relative to the total available isocyanate groups. Preferably, water alone is used to prepare the aqueous prepolymer solution, but solutes or particulates may be present, if desired. Solutes which react with the isocyanate groups will become an integral part of the hydrogel. Care should be taken with such solutes since too high a concentration may result in excessive end-capping of the prepolymer to such an extent that polymerization will be precluded. A prepolymer-aqueous solution may be prepared, with or without an organic solvent, to initiate polymerization and curing. Alternatively, the organic solvent-prepolymer solution may be coated onto the desired substrate and then contacted with water or an aqueous solution to effect polymerization and curing.

For the embodiment in which an aqueous prepolymer solution is made, the prepolymer-to-water ratio should be 1:1 to 1:20, preferably 1:5 to 1:15. Gelling time increases as the proportion of prepolymer in the aqueous solution decreases. The solution should be stirred or agitated until completely mixed.

Polymerization begins to occur spontaneously with formation of urea upon contact of the isocyanate groups of the prepolymer with the water. Catalysts or crosslinking agents are not required but are considered optional and may be used if desired. Suitable catalysts include organic tin salts (e.g., dibutyltin dilaurate) and tertiary amines. Suitable crosslinking agents include primary and secondary polyamines and polyfunctional isocyanates.

As polymerization begins to occur, gelling takes place. Prior to gelling, the prepolymer solution may be shaped, poured or handled as necessary. Where extensive or precise shaping or handling is required, an aliphatic polyisocyanate should be used in preparing the prepolymer. (As an alternative to shaping at this stage, the hydrated polymer may itself be cut to the desired size or shape.) At the gelling stage, the hydrated polymer takes on the physical form of the final cured product, forming a semisolid elastic matrix, although unreacted isocyanate groups still will be present. Gelling time may be on the order of from thirty seconds to one hour. Upon gelation, the mixture loses its ability to flow, becoming a jelly-like solid or semi-solid mass. The polymer continues curing until the chemical reaction of all residual

isocyanate groups is complete or approaches completion. Complete reaction may take hours, days or weeks, depending on the conditions and the polyisocyanate used. The curing time may be shortened by addition of chain terminating or inactivation agents, such as ethanolamine, which causes end-capping without chain extension. The final polymer product is a polyurethane.

- 5 To set the shape of the hydrated polymer, only gelation is required. However, complete or substantially complete curing is necessary in order to produce a hydrated polymer which completely resists nonspecific protein binding. Complete isocyanate reaction may be ensured by soaking the polymer in water to reduce or eliminate the availability of residual isocyanate groups, or by incorporating chain terminating agents as described above. This eliminates residual isocyanate groups which may bind proteins which come into contact with the hydrated polymer.
- 10 Gelling and curing time will vary, depending in part on the concentration of prepolymer present in the aqueous solution from which the hydrated polymer is formed. Gelling time decreases with higher prepolymer concentrations. In addition, gelling time depends on the type of polyisocyanate used in preparing the prepolymer. Aromatic polyisocyanate end-capped prepolymers will gel rapidly, usually reacting in somewhat less than one minute, although the curing time may be longer. Prepolymers capped with aliphatic polyisocyanates have a longer gelling time, typically 20 to 90 minutes,
- 15 and may take from up to several hours to several weeks for complete curing. If desired, the hydrated polymer may be subjected to a drying step.

When the polymer of this invention is prepared as a coating in the form of a thin film or a monomolecular or substantially monomolecular layer, a distinction between gelling and curing is less apparent. In this embodiment, the prepolymer-organic solvent solution is deposited on a substrate and excess organic solvent is removed. Atmospheric moisture may be sufficient for polymerization of the gel coating or layer. Water is added to promote chain extension and crosslinking of the polymer on the substrate surface. This crosslinking is necessary to stabilize the coating, which otherwise would wash off under certain conditions, such as high water flow rates, or high or low pH, for example. The coating is subjected to this water treatment for 15 minutes to 24 hours, or longer, to ensure complete or substantially complete reaction of the isocyanate groups. If desired, the coating may be treated with a chain terminating agent, such as ethanolamine, to ensure reaction of the residual isocyanate groups. The excess water may be removed by evaporation.

The surface properties of the hydrated polymer described herein are unique and offer significant advantages over conventional polymer systems. In particular, the hydrated polymers of this description are resistant to nonspecific protein adsorption. This feature avoids problems associated with undesirable protein adsorption, such as cloud formation and occlusion. As a result, the hydrated polymer products and derivatives of this invention will have longer useful lives in applications where contact with proteins is likely. Moreover, the polymers of this invention are particularly useful for applications in which conventional polymers and hydrogels are unacceptable or undesirable because of protein adsorption.

The biocompatibility of the hydrated polymers of this invention is related, at least in part, to the polymers' ability to resist protein adsorption. While not limiting the effectiveness of this invention to any specific theory, the unique qualities of these polymers are believed to relate to the use of predominantly or exclusively ethylene oxide-based diols or polyols in the formulation of the prepolymers and hydrated polymers. When the polymers of this invention are used in contact with an aqueous system, the ethylene oxide segments of the polymer attract and complex with water molecules. Consequently, the surface presented to living cells or tissues is predominantly a layer of water. This protective curtain of water renders the underlying synthetic polymeric material noninteractive with proteins. The result is a hydrated polymer which is physiologically acceptable, and which does not remove or denature proteins from the environment in which the polymer is used.

Biocompatibility, as used herein to describe the hydrated polymers of this invention, refers to the resistance to adsorption of protein and to the lack of interactiveness with physiological surfaces, as discussed above. In addition, the hydrated polymers of this invention have been demonstrated to be nontoxic to mammalian cells. Use of aliphatic polyisocyanates in preparation of the prepolymers may further enhance the biocompatibility of the hydrated polymer product since the potential degradation products of aliphatic polyisocyanates are reported to be significantly less carcinogenic than those of aromatic isocyanates. However, if aromatic polyisocyanates are used, careful washing or other means for removing any unreacted isocyanate and related amine-containing by-products generally will be sufficient to render the hydrated polymer biocompatible.

The finished hydrated polymer is water swellable and is capable of swelling to an extent that it may comprise up to 95 to 99% water. The volumetric expansion may be tenfold for polymers made with about a 1:5 prepolymer-to-water ratio. Decreasing the relative proportion of prepolymer will allow for increased volumetric expansion. Hydrated polymers made from solutions containing high concentrations of prepolymer versus water tend to form tighter polymeric compositions which are less susceptible to expansion.

The hydrated polymers of this invention are covalently extended and crosslinked and therefore are not readily soluble or degradable in aqueous systems under physiological conditions, which further increases the polymers' suitability for use with living cells or tissues. The physical integrity of the hydrated polymer is maintained when used in an

aqueous system, eliminating problems with toxicity and contamination. Moreover, these characteristics make it possible to use the hydrated polymers of this invention in aqueous systems over extended periods with minimal loss of polymer strength or integrity.

5 The prepolymers of this invention have the ability to gel large amounts of water, as described above. The hydrated polymers formed may be termed hydrogels. The polymers retain the transparency qualities of the water and may be used in applications which require transparent polymers.

The examples which follow are given for illustrative purposes and are not meant to limit the invention described herein. The following abbreviations have been used throughout in describing the invention.

10	A - Angstrom(s)
	°C - degrees Centigrade
	cm - centimeter(s)
	DMEM - Dulbecco's Modified Eagle's Medium
	DI - deionized
15	F12 - F12 cell culture medium
	gm - gram(s)
	Hg - mercury
	IDPI - isophorone diisocyanate
	IU - International unit(s)
20	M - molar
	m ² - square meter(s)
	meq - milliequivalent(s)
	mg - milligram(s)
	min - minute(s)
25	ml - milliliter(s)
	mm - millimeter(s)
	μm - micrometer
	MW - molecular weight
	ngm - nanogram(s)
30	PBS - phosphate buffered saline
	% - percent
	TM - trademark
	UV - ultraviolet
	v - volume
35	wt - weight

EXAMPLE I

(Preparation of Prepolymer A)

40 The polyol used to prepare the prepolymers of this invention, Pluracol V7 (TM) (BASF), a 7000 MW triol copolymer of ethylene oxide (75%) and propylene oxide (25%), was deionized and dried. Following this deionization procedure, 1687.46 gm Pluracol V7 was mixed with 165.0 gm isophorone diisocyanate (IDPI) and 0.93 gm Santonox R (TM) (Monsanto Chemical Co.) and heated at 70°C under dry nitrogen. Isocyanate levels were determined by addition of dibutylamine and back titration with standard acid. Fourteen days were required for the isocyanate concentration to reach 0.47 meq/gm (0.39 meq/gm = theoretical). The resulting prepolymer, designated Prepolymer A, was liquid at room temperature.

EXAMPLE II

(Preparation of Prepolymer B)

50 A prepolymer was formed by mixing 300.0 gm deionized and dried TPEG10000 (TM) (Union Carbide Corp.) with 22.0 gm IPDI and 0.16 gm Santonox R. TPEG10000 is a 10,000 MW triol prepared from 100% homopolymeric ethylene oxide. The mixture was heated at 70°C under dry nitrogen as in Example I, until isocyanate values reached 0.36 meq/gm (theoretical = 0.28 meq/gm). This prepolymer, designated Prepolymer B, formed a solid when cooled to room temperature.

EXAMPLE III

(Preparation of Prepolymer C)

5 A prepolymer was formed by mixing 403.0 gm deionized and dried TPEG20000 (TM) (Union Carbide Corp.) with 14.78 gm IPDI and 0.21 gm Santonox R. TPEG20000 is a 20,000 MW triol prepared from 100% homopolymeric ethylene oxide. To this mixture 515.0 ml acetonitrile was added to prevent solidification. The resulting mixture was heated as in Example I for eleven days until an isocyanate content of 0.147 meq/gm, corrected for solvent (theoretical = 0.145 meq/gm), was reached. The prepolymer, designated Prepolymer C, was a liquid at room temperature.

10

EXAMPLE IV

(Preparation of Prepolymer D)

15 A prepolymer was prepared as in Example I, using 293.0 gm TPEPG10000 (TM) (Union Carbide Corp.), 23.92 gm IPDI and 0.16 gm Santonox R. TPEPG10000 is a 9000 MW triol prepared from 88% ethylene oxide and 12% propylene oxide polymerization monomers. The reactants were dissolved in 293.0 ml acetonitrile and synthesis was conducted as in Example I. After thirteen days the isocyanate content was 0.43 meq/gm (theoretical = 0.31 meq/gm). The prepolymer was designated Prepolymer D.

20

EXAMPLE V

(Preparation of Prepolymer E)

25 A prepolymer was prepared as in Example I, using 572 gm BASF #46889 (a 7000 MW triol comprised of 80% ethylene oxide and 20% propylene oxide), 59.0 gm IPDI and 0.54 gm Santonox R. The reactants were dissolved in 572.0 ml acetonitrile and synthesis was performed as in Example I. After fourteen days the isocyanate content was 0.46 meq/gm (theoretical = 0.39 meq/gm). This prepolymer was designated Prepolymer E.

30 EXAMPLE VI

(Preparation of Prepolymer F)

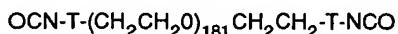
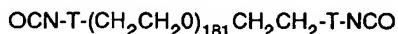
35 The prepolymer was prepared by mixing 79.0 gm Pluracol V10 (TM) (BASF) (a 22,000 MW diol comprised of 75% ethylene oxide and 25% propylene oxide), 0.24 gm trimethylolpropane and 2.94 gm IPDI. An antioxidant, Irganox 1076 (TM) (Ciba-Geigy Corp.) was added, to 0.05% of the total weight of the reactants (0.041 gm) and 150.0 ml acetonitrile was added to reduce viscosity. The synthesis was performed as in Example I. After eight days the isocyanate concentration was 0.18 meq/gm (theoretical estimated at approximately 0.24 meq/gm). This prepolymer was designated Prepolymer F.

40

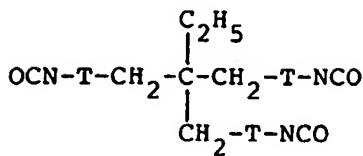
EXAMPLE VII

(Preparation of Prepolymer G)

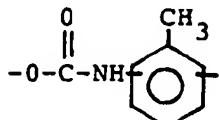
45 This prepolymer was prepared by heating to 60°C a mixture of 0.031 moles homopolymer polyethylene glycol (~8000 MW) and 0.015 moles trimethylolpropane. The preheated mixture was added to 0.11 moles toluene diisocyanate (80% toluene-2,4-diisocyanate/20% toluene-2,6-diisocyanate isomer blend) over a period of about one hour, with stirring. After an additional hour of stirring, the isocyanate concentration reached a substantially constant value of 0.39 meq/gm (theoretical = 0.40 meq/gm). This prepolymer was designated Prepolymer G and had the following idealized average composition:



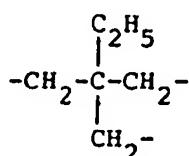
55



where T represents



(the toluene diisocyanate urethane reaction moiety), and

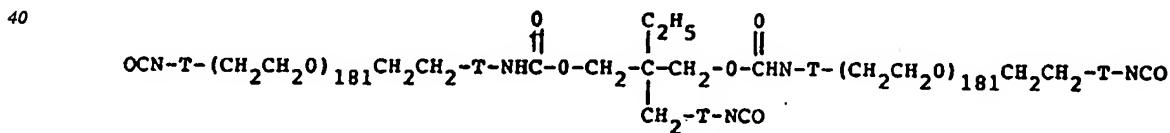


represents the trimethylolpropane reaction moiety. The calculated average composition of the Prepolymer G mixture comprised two moles of isocyanate-capped linear polymer of about 8350 MW for each mole of trifunctional isocyanate-capped crosslinker of about 656 MW. In effect, it is expected that when Prepolymer G is mixed with, and polymerized with, water or another aqueous liquid, it would react as though it has an effective molecular weight of about 17,000, or the sum of the weights of the three species depicted schematically above.

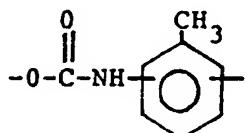
EXAMPLE VIII

30 (Preparation of Prepolymer H)

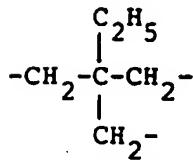
This prepolymer was prepared by heating to 60°C a mixture of 0.04 moles homopolymer polyethylene glycol (~8000 MW) and 0.02 moles trimethylolpropane. The preheated mixture was added to 0.10 moles toluene diisocyanate (80% toluene-2,4-diisocyanate/20% toluene-2,6-diisocyanate isomer blend) over a period of about one hour, with stirring. The difference in concentration of ingredients yielded a different prepolymer than that obtained in Example VII. After an additional hour of stirring, the isocyanate concentration reached a substantially constant value of 0.20 meq/gm (theoretical = 0.18 meq/gm). This prepolymer was designated Prepolymer H and had the following idealized average structure:



45 where T represents



(the toluene diisocyanate urethane reaction moiety), and



represents the trimethylolpropane reaction moiety. The calculated average molecular weight for Prepolymer H is about 17,000.

10

EXAMPLE IX

(Preparation of Prepolymer J)

15 A prepolymer was formed by repeating the preparation of Example I, except that the IPDI was replaced by an equivalent molar amount of toluene diisocyanate (80% toluene-2,4-diisocyanate/20% toluene-2,6-diisocyanate isomer blend). After heating for about seven hours, the isocyanate values reached 0.43 meq/gm (theoretical = 0.40 meq/gm). This prepolymer, a liquid at room temperature, was designated Prepolymer J.

20

EXAMPLE X

(Preparation of Hydrated Polymer A)

25 Five grams of Prepolymer A (see Example I) were mixed thoroughly with 25.0 gm water with a stirring rod for about two to four minutes, until all the Prepolymer A was in solution. The solution was allowed to stand undisturbed for one hour at room temperature while the gelling reaction occurred and then was kept in a closed container at room temperature overnight to prevent water evaporation and to permit essentially complete chemical reaction of all isocyanate end groups. The polymer, designated Hydrated Polymer A, was removed intact and stored wet at room temperature in a closed container.

30

EXAMPLE XI

(Preparation of Hydrated Polymer J)

35 Hydrated polymer gels were prepared by mixing one part Prepolymer J with five parts water, on a weight basis. Gelation occurred within about 45.0 seconds at ambient temperatures. The gels were cured by standing overnight under ambient conditions.

40

EXAMPLE XII

(Preparation of Hydrated Polymer Coatings A-E)

Hydrated polymer coatings were formed on particulate silica (particle size = 10.0 μm ; surface area = 250 m^2/gm), using Prepolymers A-E of the above Examples. The following procedure was used for each prepolymer.

45 On a sintered glass filter was placed 5.0 gm silica, and 50.0 ml of a 5.0% Prepolymer in acetonitrile solution was pulled through the silica bed with a vacuum. The solution was recovered and was passed repeatedly over the silica bed until the solvent had evaporated. Residual solvent was removed under vacuum for one hour at ambient temperatures. The coated particles were placed in a water bath at ambient temperatures for 17 hours to effect crosslinking and polymerization, then dried under vacuum at 50°C for 17 hours.

50 The extent of coating achieved with each of the Hydrated Polymers A-E under these conditions was determined by thermal degradation analysis. For each polymer, 100.0 mg of coated particles were weighed before and after heating for five hours at 800°C. Table I shows the weight percent attributable to the hydrated polymer coating for each sample.

55

TABLE I

Hydrated Polymer Coatings	
Pre polymer	Wt.% Loss on Heating
A	10.0
B	13.7
C	8.5
D	6.5
E	12.5

EXAMPLE XIII

15 (Hydrated Polymer Coating Stability)

The stability and durability of hydrated polymer coatings of this invention were compared with similarly obtained coatings of the precursor polyol. The coatings indicated in Table II were obtained by allowing solvent to evaporate from a suspension of silica, the coating substance and solvent. The silica used here had a 500 Angstrom pore diameter and a particle size of 20-45 µm. The suspension was formed by mixing 2.5 gm silica and 25 ml of 5% prepolymer or polyol in dichloromethane. The solvent was allowed to evaporate under ambient conditions. By using the evaporation procedure of this experiment, coating weights of about 25-30% were obtained, as compared with about 6-14% for the coating method described in Example XII.

Coating durability was assessed by comparing the coating weight following preparation with the coating weight following washing as described here. All coating weights were measured by the thermal analysis method of Example XII. The coated samples were washed with four 25.0 ml portions of 0.05M sodium phosphate (pH 8.0) then with four 25.0 ml portions of 0.1% trifluoroacetic acid in a 60/40 solution of isopropanol/water. The results, shown in Table II, demonstrate the substantially improved coating stability obtained by crosslinking on the substrate surface in the presence of water.

30 TABLE II

Coating Stability		
Coating	Washings	%Wt. Loss on Heating
Precursor polyol	None	26.40 ± 0.28
Precursor polyol	As described	2.97 ± 0.18
Prepolymer A	None	30.53 ± 1.14
Prepolymer A	As described	28.80 ± 0.42

40 EXAMPLE XIV

(Gelling Time)

The rate of gel formation as a function of prepolymer-to-water ratio was investigated by mixing varying proportions of water and Prepolymer A and allowing the mixtures to stand at ambient temperatures with no further agitation. Table III shows the times required for gelling, which was determined by visual examination.

50 TABLE III

Gelling Time as a Function of Prepolymer Concentration		
Prepolymer:Water	%Prepolymer	Gelling Time (min)
1:1	50.0	19.0
1:2	33.3	21.0
1:3	25.0	23.0
1:4	20.0	24.0
1:5	16.7	28.0

TABLE III (continued)

Gelling Time as a Function of Prepolymer Concentration		
Prepolymer:Water	%Prepolymer	Gelling Time (min)
1:6	14.3	32.0
1:7	12.5	33.0
1:8	11.1	41.0
1:9	10.0	40.0
1:10	9.1	38.0
1:15	6.3	57.0
1:20	4.8	85.0

EXAMPLE XV

(Resistance to Protein Binding)

To demonstrate the ability of the hydrated polymers of this invention to resist nonspecific protein binding or adsorption, a protein adsorptive surface was coated with prepolymer, which then was polymerized. Silica was chosen as the surface to be coated due to its ability to bind large amounts of protein. One gram of silica (particle size = 10.0 μm , surface area = 250.0 m^2/gm) was placed in a glass fritted filtering funnel. Fifty milliliters of a 5.0% solution of Prepolymer A in dry methylene chloride was passed over the bed repeatedly, under vacuum, until all solvent had evaporated. The coated silica was dried at 25°C under vacuum for 16 hours, then placed in water overnight at 25°C to allow polymerization to occur.

To determine the extent of protein binding, one gram of uncoated silica (control) and one gram of silica coated with the hydrated polymer each were mixed with 10.0 ml of 1.0 mg/ml hemoglobin in phosphate buffered saline ("PBS") (0.05M sodium phosphate, pH 7.0, 0.3M sodium chloride) for one hour at 25°C. The control and coated silicas were collected by filtration and were washed with PBS until 50.0 ml of the wash buffer were collected for each silica sample. Protein determinations were performed on each wash solution using the BioRad dye binding assay (BioRad Laboratories). The uncoated silica control was found to bind all of the 10.0 mg protein added. Protein binding to the silica coated with the hydrated polymer of this invention was below the limits of detection for this assay. Coating a surface normally adsorptive to protein with a polymer of this invention therefore reduced protein binding by >99%.

EXAMPLE XVI

(Resistance to Protein Binding)

Hydrated polymer coatings prepared from Prepolymers A-E were tested for resistance to protein binding. Silica (20-45 μm particle size; pore diameter = 500A) was coated with each Prepolymer and polymerized as described in Example XII. Protein binding to the coated silica was determined by incubating 0.2 gm silica with 50.0 mg hemoglobin in 10.0 ml phosphate buffered saline (.01M sodium phosphate, pH7) for one hour. The amount of hemoglobin bound to the polymer-coated silica then was measured using the BioRad dye binding reagent (BioRad Laboratories) in the presence of 80% sucrose in 0.05 M sodium borate (pH 7.0). After five minutes, the absorbance at 595 nm was measured and compared with an uncoated silica control. The protein rejection shown in Table IV was expressed as a percent of the control.

TABLE IV

Rejection of Protein Binding	
Prepolymer Coating	Rejection of Protein Binding, %
A	96.0
B	99.9
C	97.8
D	92.1
E	98.7

EXAMPLE XVII

(Hydrated Polymer Biocompatibility)

5 Test samples of hydrated polymer were prepared by mixing ten parts (v/w) Dulbecco's Modified Eagle's Medium (DMEM) with one part Prepolymer A (see Example I). After mixing completely, several aliquots of the solution were transferred to 10 cm polystyrene petri dishes in such a manner that the entire surface was not covered but, rather, puddles or droplets were formed. The dishes were left at ambient temperatures for 30 minutes. After polymerization was complete, approximately 20% of the surface of each dish was covered with hydrated polymer. The dishes were
 10 sterilized by UV irradiation for 48 hours.

15 The cells used to test biocompatibility in this example were the LCC-PKI line (porcine kidney epithelial cell line obtained from American Type Culture Collection) which proliferate as a monolayer. At confluence, these cells cease proliferation and begin differentiation. The hallmark of differentiation by this cell line is the formation of domes, or raised groupings of cells, caused by accumulation of a fluid pocket under the cells as a result of vectorial transport of water and ions.

20 The petri dishes prepared above were inoculated with cells at near confluent densities in a suspension of culture medium (3:1 solution of DMEM:F12 cell culture medium) containing 1.0% fetal bovine serum and penicillin (100 IU/ml), streptomycin (100 µg/ml) and amphotericin B (250 ng/ml). The dishes were incubated at 37°C. After 24 hours, a monolayer of cells had spread on the polystyrene surface. No cells had attached to the hydrated polymer but cells
 25 were visible on the polystyrene surface just adjacent to the polymer. After one week of culture at 37°C, the hydrated polymer surface remained free of cells. Cells growing on the polystyrene surface appeared identical to those in control cultures (with no hydrated polymer) and exhibited dome formation. It therefore is concluded that no toxic substances and/or inhibitors of cellular differentiation were present in the cultures containing the hydrated polymer.

30 The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

35 **Claims**

1. A crosslinked hydrophilic, biocompatible hydrated polymer gel prepared by reacting together water and a prepolymer in a prepolymer-to-water ratio of 1:1 to 1:20, said prepolymer being prepared by:
 - (a) selecting diols or polyols having molecular weights of 7000 to 30,000, at least 75% of which are oxyethylene-based, and
 - (b) reacting said diols or polyols with polyisocyanate at an isocyanate-to-hydroxyl ratio of 1.8 to 2.2 so that essentially all of the hydroxyl groups of said diols or polyols are capped with polyisocyanate and the resulting prepolymer has an isocyanate concentration of 0.1 to 0.47 meq/g.
2. The hydrated polymer gel of claim 1 in which at least 90% of said prepolymer units are polyisocyanate-capped oxyethylene-based diols or polyols.
3. The hydrated polymer gel of claim 1 or 2 in which at least 95% of said prepolymer units are polyisocyanate-capped oxyethylene-based diols or polyols.
4. The hydrated polymer gel of any of claims 1 to 3 in which the molecular weight of said diols or polyols prior to capping with polyisocyanate is at least 10,000.
5. The hydrated polymer gel of any of claims 1 to 4 in which the molecular weight of said diols or polyols prior to capping with polyisocyanate is from 10,000 to 20,000.
6. The hydrated polymer gel of any of claims 1 to 5 which comprise an antioxidant agent.
7. The hydrated polymer gel of any of claims 1 to 6 in which said prepolymer is dissolved in an organic solvent selected from acetonitrile, dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, dioxane, acetone, methyl ethyl ketone, methanol, ethanol, 2-propanol, dichloromethane, or mixtures thereof, prior to reacting with water.

8. The hydrated polymer gel of any of claims 1 to 7 which is in the form of a coating, and is prepared by depositing the prepolymer-organic solvent solution on a coatable substrate, removing excess organic solvent and then reacting the prepolymer with water to promote crosslinking on the substrate surface.
- 5 9. The hydrated polymer gel of any of claims 1 to 8 in which said prepolymer-to-water-ratio is between 1:5 to 1:15.
- 10 10. The hydrated polymer gel of any of claims 1 to 9 which is formed by mixing together water and said prepolymer, coating the resulting solution onto a coatable substrate prior to gelation of said solution, and removing excess water by evaporation.
- 10 11. A prepolymer for preparing a hydrophilic, biocompatible polymer gel characterized by transparency and by resistance to nonspecific protein adsorption, said prepolymer consisting of oxyethylene-based diols or polyols having molecular weights of about 7000 to about 30,000, said diols or polyols being reacted with polyisocyanate at an isocyanate-to-hydroxyl ratio of 1.8 to 2.2 so that essentially all of the hydroxyl groups are capped with polyisocyanate, and said prepolymer having an isocyanate concentration of 0.1 to 0.47 meq/g and having the ability to gel water upon polymerization in prepolymer-to-water ratios of 1:1 to 1:20.
- 15 12. Use of a hydrophilic, biocompatible hydrated polymer gel according to any of claims 1 to 10 or a prepolymer according to claim 11 for coating of substrates and surfaces useful in the field of biomedical applications.
- 20 13. Use of claim 12, wherein said substrate is a petri dish or particulate silica.
14. Petri dish coated with a hydrophilic, biocompatible hydrated polymer according to any of claims 1 to 10.
- 25 15. Silica particles coated with a hydrophilic, biocompatible hydrated polymer according to any of claims 1 to 10.

Patentansprüche

- 30 1. Vernetztes, hydrophiles, bioverträgliches, hydratisiertes Polymergel, das hergestellt worden ist, indem Wasser und ein Präpolymer in einem Präpolymer-zu-Wasser-Verhältnis von 1:1 bis 1:20 miteinander umgesetzt worden sind, wobei das Präpolymer hergestellt worden ist, indem
- 35 (a) Diole und Polyole mit Molekulargewichten von 7 000 bis 30 000, von denen mindestens 75% auf Oxyethylen basieren ausgewählt worden sind, und
- (b) die Diole oder Polyole mit Polyisocyanat in einem Isocyanat-zu-Hydroxyl-Verhältnis von 1,8 bis 2,2 so umgesetzt worden sind, daß im wesentlichen alle von den Hydroxylgruppen der Diole oder Polyole mit Polyisocyanat verkappt worden sind und das resultierende Präpolymer eine Isocyanatkonzentration von 0,1 bis 40 0,47 meq/g besessen hat.
2. Hydratisiertes Polymergel nach Anspruch 1, bei dem mindestens 90% der Präpolymereinheiten mit Polyisocyanat verkappte, auf Oxyethylen basierende Diole oder Polyole sind.
- 45 3. Hydratisiertes Polymergel nach Anspruch 1 oder 2, bei dem mindestens 95% der Präpolymereinheiten mit Polyisocyanat verkappte, auf Oxyethylen basierende Diole oder Polyole sind.
4. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 3, bei dem das Molekulargewicht der Diole oder Polyole vor dem Verkappen mit Polyisocyanat mindestens 10 000 beträgt.
- 50 5. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 4, bei dem das Molekulargewicht der Diole oder Polyole vor dem Verkappen mit Polyisocyanat 10 000 bis 20 000 beträgt.
6. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 5, das Antioxidans umfaßt.
- 55 7. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 6, bei dem das Präpolymer vor der Umsetzung mit Wasser in einem organischen Lösungsmittel ausgewählt aus Acetonitril, Dimethylformamid, Dimethylsulfoxid, Tetrahydrofuran, Dioxan, Aceton, Methylethylketon, Methanol, Ethanol, 2-Propanol, Dichlormethan oder Mischungen

derselben gelöst wird.

8. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 7, das in Form einer Beschichtung vorliegt und hergestellt worden ist, indem die Präpolymer/organisches Lösungsmittel-Lösung auf einem beschichtbaren Substrat aufgebracht worden ist, überschüssiges organisches Lösungsmittel entfernt worden ist und dann das Präpolymer mit Wasser umgesetzt worden ist, um eine Vernetzung auf der Substratoberfläche zu fördern.
9. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 8, bei dem das Präpolymer-zu-Wasser-Verhältnis zwischen 1:5 bis 1:15 liegt.
10. Hydratisiertes Polymergel nach einem der Ansprüche 1 bis 9, das gebildet worden ist, indem Wasser und das Präpolymer miteinander gemischt worden sind, die resultierende Lösung vor der Gelierung dieser Lösung auf ein beschichtbares Substrat beschichtet worden ist und überschüssiges Wasser durch Verdampfung entfernt worden ist.
11. Präpolymer für die Herstellung eines hydrophilen, bioverträglichen Polymergeles, das durch Transparenz und Widerstandsfähigkeit gegenüber unspezifischer Proteinadsorption gekennzeichnet ist, wobei das Präpolymer aus auf Oxyethylen basierenden Diolen oder Polyolen mit Molekulargewichten von etwa 7 000 bis etwa 30 000 besteht, die Diole oder Polyole mit Polyisocyanat in einem Isocyanat-zu-Hydroxyl-Verhältnis von 1,8 bis 2,2 so umgesetzt worden sind, daß im wesentlichen alle von den Hydroxylgruppen mit Polyisocyanat verkappt sind, und das Präpolymer eine Isocyanatkonzentration von 0,1 bis 0,47 meq/g und die Fähigkeit aufweist, Wasser bei Polymerisation in Präpolymer-zu-Wasser-Verhältnissen von 1:1 bis 1:20 zu gelieren.
12. Verwendung eines hydrophilen, bioverträglichen, hydratisierten Polymergeles gemäß einem der Ansprüche 1 bis 10 oder eines Präpolymers gemäß Anspruch 11 zur Beschichtung von Substraten und Oberflächen, die auf dem Gebiet von biomedizinischen Anwendungen brauchbar sind.
13. Verwendung nach Anspruch 12, bei der das Substrat eine Petrischale oder teilchenförmiges Siliciumdioxid ist.
14. Petrischale, die mit einem hydrophilen, bioverträglichen, hydratisierten Polymer gemäß einem der Ansprüche 1 bis 10 beschichtet ist.
15. Siliciumdioxidteilchen, die mit einem hydrophilen, bioverträglichen, hydratisierten Polymer gemäß einem der Ansprüche 1 bis 10 beschichtet sind.

Revendications

1. Gel d'un polymère hydraté, hydrophile, biocompatible, réticulé, préparé par réaction d'eau et d'un prépolymère à un rapport prépolymère à eau de 1:1 à 1:20, ledit prépolymère étant préparé par :
 - (a) sélection de diols ou polyols ayant des poids moléculaires de 7000 à 30000, dont au moins 75% sont à base d'oxyéthylène, et
 - (b) réaction desdits diols ou polyols avec du polyisocyanate à un rapport isocyanate à hydroxyle de 1,8 à 2,2 de manière qu'essentiellement tous les groupes hydroxyles desdits diols ou polyols soient coiffés par des polyisocyanates et que le prépolymère résultant ait une concentration en isocyanate de 0,1 à 0,47 meq/g.
2. Gel de polymère hydraté selon la revendication 1 où au moins 90% desdites unités de prépolymère sont des diols ou polyols à base d'oxyéthylène coiffés de polyisocyanate.
3. Gel de polymère hydraté de la revendication 1 ou 2 où au moins 95% desdites unités du prépolymère sont des diols ou polyols à base d'oxyéthylène coiffés de polyisocyanate.
4. Gel de polymère hydraté selon l'une des revendications 1 à 3, où le poids moléculaire desdits diols ou polyols avant coiffage avec du polyisocyanate est d'au moins 10000.
5. Gel de polymère hydraté selon l'une des revendications 1 à 4, où le poids moléculaire desdits diols et polyols avant coiffage avec du polyisocyanate est de 10000 à 20000.

6. Gel de polymère hydraté selon l'une des revendications 1 à 5, qui comprend un agent antioxydation.
7. Gel de polymère hydraté selon l'une des revendications 1 à 6 où ledit prépolymère est dissous dans un solvant organique sélectionné parmi l'acétonitrile, le diméthyl formamide, le diméthyl sulfoxyde, le tétrahydrofurane, le dioxane, l'acétone, la méthyl éthyl cétone, le méthanol, l'éthanol, le 2-propanol, le dichlorométhane, ou des mélanges de ceux-ci, avant réaction avec l'eau.
8. Gel de polymère hydraté selon l'une des revendications 1 à 7 qui est sous la forme d'un revêtement et qui est préparé en déposant la solution d'un solvant organique du prépolymère sur un substrat pouvant être enduit, en retirant le solvant organique en excès puis en faisant réagir le prépolymère avec de l'eau pour favoriser la réticulation à la surface du substrat.
9. Gel de polymère hydraté selon l'une des revendications 1 à 8 où ledit rapport prépolymère à eau est compris entre 1:5 et 1:15.
10. Gel de polymère hydraté selon l'une des revendications 1 à 9 qui est formé en mélangeant ensemble de l'eau et ledit prépolymère, en enduisant la solution résultante sur un substrat pouvant être enduit, avant gélification de ladite solution et en retirant l'eau en excès par évaporation.
11. Prépolymère pour la préparation d'un gel d'un polymère hydrophile biocompatible, caractérisé par la transparence et par la résistance à une absorption de protéines non spécifiques, ledit prépolymère consistant en diols ou polyols à base d'oxyéthylène ayant des poids moléculaires d'environ 7000 à environ 30000, lesdites diols ou polyols réagissant avec du polyisocyanate à un rapport isocyanate à hydroxyle de 1,8 à 2,2 de manière qu'essentiellement tous les groupes hydroxyles soient coiffés par du polyisocyanate et ledit prépolymère ayant une concentration en isocyanate de 0,1 à 0,47 meq/g et ayant l'aptitude de gélifier l'eau lors d'une polymérisation à des rapports prépolymère à eau de 1:1 à 1:20.
12. Utilisation d'un gel d'un polymère hydrophile biocompatible hydraté selon l'une des revendications 1 à 10 ou d'un prépolymère selon la revendication 11 pour enduire des substrats et des surfaces utiles dans le domaine des applications biomédicales.
13. Utilisation de la revendication 12 où ledit substrat est une boîte de Pétri ou de la silice particulière.
14. Boîte de Pétri enduite d'un polymère hydrophile, biocompatible, hydraté, selon l'une des revendications 1 à 10.
15. Particules de silice enduites d'un polymère hydrophile, biocompatible, hydraté, selon l'une des revendications 1 à 10.

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